Intranasal Antiviral Drug Delivery and Coronavirus Disease 2019 (COVID-19): A State of the Art Review

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Abstract

Objective
To provide a state of the art review of intranasal antiviral drug delivery and to discuss current applications, adverse reactions, and future considerations in the management of coronavirus disease 2019 (COVID-19).

Data Sources
PubMed, Embase, and Clinicaltrials.gov search engines.

Review Methods
A structured search of the current literature was performed of dates up to and including April 2020. Search terms were queried as related to topics of antiviral agents and intranasal applications. A series of video conferences was convened among experts in otolaryngology, infectious diseases, public health, pharmacology, and virology to review the literature and discuss relevant findings.

Conclusions
Intranasal drug delivery for antiviral agents has been studied for many years. Several agents have broad-spectrum antiviral activity, but they still require human safety and efficacy trials prior to implementation. Intranasal drug delivery has potential relevance for future clinical trials in the settings of disease spread prevention and treatment of SARS-CoV-2 and other viral diseases.

Implications for Practice
Intranasal drug delivery represents an important area of research for COVID-19 and other viral diseases. The consideration of any potential adverse reactions is paramount.

Keywords
coronavirus, COVID-19, antiviral agents, nasal, nasopharynx, public health, severe acute respiratory syndrome coronavirus 2, otolaryngology

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This is the author's manuscript of the article published in final edited form as:

Higgins, T. S., Wu, A. W., Illing, E. A., Sokoloski, K. J., Weaver, B. A., Anthony, B. P., ... & Ting, J. Y. (2020). Intranasal antiviral drug delivery and coronavirus disease 2019 (COVID-19): a state of the art review. Otolaryngology–Head and Neck Surgery, 163(4), 682-694. https://doi.org/10.1177/0194599820933170

The rapid spread of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in the immunologically naïve human population has led to a global pandemic. SARS-CoV-2 is spread primarily through airborne droplet and contact transmission with contaminated fomites. While SARS-CoV-2 particles may persist on surfaces for several days, as enveloped viruses, they are sensitive to desiccation and mild detergent disinfection.[1] Small population studies indicate that between 6% and 88% of SARS-CoV-2 infections do not result in overt disease.[2-4] The impact of asymptomatic or subclinical individuals to public health is clear, with up to 44% of infected individuals having contracted the virus from asymptomatic persons.[5] Individuals who display clinical symptoms of SARS-CoV-2 infection, or coronavirus disease 2019 (COVID-19), exhibit a range of symptom severity, with high case fatality rates in the elderly, immunocompromised patients, and those with comorbid diabetes and cardiac, pulmonary, and immunocompromised conditions.[6]

The nasal cavity and nasopharynx contain some of the highest viral loads in the body, and viral loads are similar in symptomatic and asymptomatic individuals. Accordingly, these “silent spreaders” may unknowingly contribute to the exponential growth of disease, as nasal secretions contain spreadable virus, and contagiousness appears to be highest before or shortly after symptom onset.

Current strategies to mitigate the pandemic have focused on public health initiatives, such as social distancing, community hygiene awareness, testing and tracing, and travel restrictions. Intranasal delivery of antiviral drugs or agents may provide an additional option for preventing disease transmission, treating the nasal disease, and providing perioperative antisepsis. This article summarizes our findings for the potential role of studying topical intranasal delivery of drugs and agents known to have antiviral properties in SARS-CoV-2.

Methods

A search of PubMed, Embase, and Clinicaltrials.gov was conducted to identify relevant peer-reviewed English articles related to intranasal application of drugs and agents with antiviral properties. A multidisciplinary team of specialists in the areas of otolaryngology, infectious diseases, public health, pharmacy, and virology was assembled to review and

summarize the literature. A series of video conferences was held to interpret the findings and discuss potential applications of intranasal application of antiviral agents in the setting of the COVID-19 pandemic. The panel discussed several topics relevant for consideration in intranasal antiviral drug therapy (**Figure 1**). Agents were assessed for evidence of antiviral activity, in SARS-CoV-2 and other viruses, and for efficacy or potential feasibility in human intranasal use. Potential intranasal adverse reactions were evaluated—specifically, mucosal or skin irritation, smell and taste disturbance, headaches, allergic reactions, nasal bleeding, fungal infection or colonization, and rhinosinusitis. Additional items of discussion included adequacy of mechanisms of target or viral cell infiltration, routes of delivery, medium suspension, additives to enhance mucosal or cellular absorption of the agents, and the reliability of compounding these substances.

Discussion

Viral Structure and Mechanism

Coronaviruses, such as SARS-CoV-2, are enveloped positive-sense RNA viruses with a genome length of approximately 30,000 nucleotides encoding 16 nonstructural proteins and at least 4 main structural proteins, although the absolute number varies among the members of Coronavirinae (**Figure 2**).[7] Architecturally, coronavirus particles are spherical with an average diameter of 125 nm, from which the projection of the spike glycoproteins create a crown-like appearance responsible for the name of the genus. In addition to the spike glycoproteins, coronavirus particles consist of the E and M integral membrane proteins, a host-derived lipid envelope, and the helical viral nucleocapsid consisting of the N protein and the viral genomic RNA.

As summarized in **Figure 3**, the coronavirus cellular viral life cycle begins with the attachment of the viral particle to the host cell via the viral spike glycoprotein.[8] The cellular receptor involved in viral entry varies among the members of Coronavirinae; however, the SARS-CoV-2 virus, in addition to the original SARS virus (SARS-CoV-1) and the endemic human coronavirus HCoV-NL63, utilizes the human angiotensin-converting enzyme 2 protein as its primary receptor.[9] The entry of the virus into the host cytoplasm requires a series of 2 proteolytic cleavage events of the spike glycoprotein to reveal the fusion peptide, which mediates the fusion of the viral and cellular lipid

bilayers. The delivery of the viral RNA into the cytoplasm results in the expression of the viral replicase complex, which consists of 16 nonstructural proteins encoded by the genomic RNA. Within the viral replication compartment, viral RNA synthesis produces a nested set of mRNA transcripts produced via a complex discontinuous RNA synthesis mechanism, which produces complementary negative-sense RNA templates. The nested mRNAs produce the remainder of the viral structural proteins, and progeny viral genomes are produced by way of continuous viral RNA synthesis. The formation of new viral nucleocapsids occurs in the cytoplasm of the infected cells, and mature viral particles are budded into the ERGIC (endoplasmic reticulum–Golgi intermediate complex) via an interaction between the ERGIC membrane–associated M protein and the N protein of the nucleocapsid. The mature viral particles are trafficked to the cell membrane in smooth-walled vesicles and released to the extracellular space.

To date, 7 coronaviruses capable of infecting humans have been identified and account for 5% to 10% of acute respiratory infections. Most endemic coronaviruses cause self-limiting upper respiratory infections; however, SARS-CoV, SARS-CoV-2, and Middle Eastern respiratory syndrome coronavirus (MERS-CoV) have notably high mortality rates.[7] Transmission of SARS-CoV-2 appears to occur primarily through respiratory droplets,[6] with secondary surface contact transmission and aerosol transmission possible. The incubation time is typically 3 to 7 days, with up to 2 weeks between time of infection and symptoms. This long asymptomatic phase is thought to contribute to the large basic reproduction number (R0) of 2.5 to 3.[10] Viral shedding has been detected in multiple anatomic sites, including the nasal cavities, nasopharynx, sputum, oropharynx, bronchial fluid, and stool.[11] However, the nasopharynx had a much higher detection rate than the oropharynx.[12]

Agents With Antiviral Capability

While no drug has been developed to specifically treat the SARS-CoV-2 virus, a few agents have been found to inactivate SARS-CoV-2 on surfaces, including ultraviolet (UV) radiation, heat, ether, ethanol, and isopropanol.[6] Other agents have been studied with other viruses. **Table 1** shows a summary of the antiviral agents discussed.

The World Health Organization (WHO) guidelines on hand hygiene in health care contain 2 alcohol-based formulations: ethanol and isopropanol.[13] These compounds are fast acting, inexpensive, and broad spectrum, previously showing the ability to inactivate SARS-CoV[14] and MERS-CoV.[15] WHO recommends the use of at least 60% ethanol or 70% isopropanol in hand sanitizer formulations.[16] However, there is evidence that both alcohols inactivate the SARS-CoV-2 down to a concentration of 30%.[17]

Intranasal application of alcohol formulations was studied in a placebo-controlled randomized controlled trial (RCT) of 387 health care workers.[18] Health care workers colonized with nasal *Staphylococcus aureus* were swabbed intranasally 3 times a day with 70% ethanol combined with natural oil emollients and the preservative benzalkonium chloride or placebo. Antiseptic use reduced *S aureus* colony-forming units by a median of 99% ($P < .001$) as compared with placebo. The participants reported no adverse effects during the study.

Povidone-Iodine

Povidone-iodine (PI) has rapid bactericidal and virucidal activity, including against SARS-CoV and MERS-CoV.[19] It is widely available in the clinical settings and has been utilized as a skin disinfectant as well as an oral wash or gargle rinse. 3M developed and evaluated an intranasal formulation application (PI solution, 5% wt/wt [0.5% available iodine]; United States Pharmacopeia) to the anterior nares. A blinded expert grader's assessment of the level of intranasal skin erythema and edema in 30 patients demonstrated no significant irritation by the Draize scale. Formulations of 5% to 10% PI have been evaluated intranasally with regard to potential side effects, and results have shown no gross injury, though ciliotoxicity has been demonstrated in vitro at these concentrations.[20] An RCT of nasal application of 10% PI, 5% PI, or placebo preoperatively for arthroscopic surgery for methicillin-resistant *S aureus* prophylaxis found equal rates of nasal irritation.[21] An in vitro study of free iodine of PI showed an association between free iodine concentration and virucidal efficacy.[22] However, a study of 5% and 10% PI applied to ciliated human respiratory epithelial cells showed ciliotoxicity.[23] Lower-concentration formulations (0.5% PI [Nasodine]) applied in vitro to air-liquid interface cultures of primary human nasal epithelial cells were found to lack cytotoxicity or ciliotoxic effect.[24] Calls for the consideration of PI application intranasally

or orally has been advocated as a preventative for patients and health care workers involved in head and neck oncologic care who are at risk of COVID-19 exposure.[25,26] Aspiration pneumonitis has been reported following surgery using oral PI as well as staining of the teeth and tongue.[27] A search of Clinicaltrials.gov revealed that a few study groups initiated protocols to evaluate intranasal or intraoral formulations of PI for SARS-CoV-2.[28-31]

Carrageenan

Carrageenan is a polysaccharide extracted from red seaweed that is widely used as a thickening agent for food. In vitro and animal studies demonstrate that carrageenan shows antiviral properties to human rhinovirus and influenza A and prevents viral attachment to host cells without systemic absorption or nasal mucosal penetration. Four placebo-controlled RCTs evaluated iota-carrageenan nasal spray in the treatment of respiratory viral infections (including rhinovirus, enteroviruses, and influenza) with variable reduction in symptoms and viral loads versus placebo saline spray.[32,33] Formulations of nasal sprays containing carrageenan are available over the counter, but the Food and Drug Administration (FDA) currently has approved this agent only as a food additive permitted for human consumption.

Acid-Buffered Saline

Acidic pH is frequently used for virus inactivation. Acidic solutions are commonly used in the pharmaceutical industry to inactivate viruses in the isolation of viral proteins and for cleaning and prevention of infection.[34,35] Acid-buffered saline has been investigated as a topical therapy for various upper respiratory viruses, showing inactivation of influenza A, decreased symptoms and viral shedding of influenza A, reduced viral shedding of human rhinovirus with the use of solutions and nasal gels, and reduced symptom severity and duration of illness in the common cold.[34,36] Unfortunately, SARS-CoV-2 has been shown to be highly stable in a range of pH environments, limiting the viability of acidic therapies as options against this virus.[1]

Hypertonic Saline

Hypertonic saline may reduce symptoms of various upper respiratory viruses as well as potentially decrease viral shedding and promote inactivation.[37,38] Ramalingam et al demonstrated via in vitro studies that increasing the availability of NaCl may facilitate the innate immune response in nonmyeloid cells via an increase in intracellular hypochlorous acid levels.[38] In an RCT of hypertonic saline irrigation and gargling for the common cold, Ramalingam et al found that the use of hypertonic saline reduced symptom severity, length of illness, intrahousehold transmission, and viral shedding.[37] Meta-analyses have shown good tolerability with some reports of nasal irritation, headache, and epistaxis.[39]

Hydrogen Peroxide

Hydrogen peroxide (H_2O_2) has long been known to cause viral inactivation, and H_2O_2 0.5% efficiently deactivates SARS-CoV-2 on surfaces.[40,41] While H_2O_2 is commonly used for surface, surgical, and oral disinfection,[40] there are currently no human clinical trials demonstrating the safety or efficacy of intranasal application of H_2O_2.

Probiotics

The use of ingested oral probiotics has been evaluated in the current COVID-19 pandemic, but the evidence of its use is from small case series and correspondences, and experts concluded that even if oral probiotics were useful, they were unlikely to have a direct effect on the severe acute respiratory syndrome that most patients with COVID-19 present.[42] However, there is evidence that the nasal and gastrointestinal microbiomes are important factors in the innate immune system and particularly in the defense against respiratory viral pathogens. Nasal microbiota clusters were found associated with host inflammatory response, viral load, and symptom severity in rhinovirus.[43] The *Corynebacterium*-rich cluster of patients had overall reduced symptoms during rhinovirus infection despite the addition of oral probiotics not significantly changing the host microbiome (nasal and gastrointestinal). *Corynebacterium* was also found to be protective against respiratory

syncytial virus infection in an in vivo mouse model.[44] Also, in a mouse model, Zelaya et al found that *Lactobacillus* introduced nasally helped prevent influenza pulmonary damage and inflammation.[45] While the effects of orally administered probiotics on a variety of viruses has been studied, we found no studies directly investigating the introduction of intranasal probiotics for the treatment of human upper respiratory virus infections. Further studies on nasal and oral administration of probiotics are warranted for COVID-19 and other upper respiratory viral infections.

Surfactants/Shampoo

Surfactants and, in particular, baby shampoo have been studied most extensively in chronic rhinosinusitis. Most studies have evaluated potential bactericidal and antibiofilm effects.[46] We found no studies that evaluated surfactant application to the nasal cavity and its ability to prevent or diminish viral infection. However, intrinsic pulmonary surfactant has been found to be an important part of our innate immune system, and its use was recently shown to help prevent several respiratory viruses, such as H1N1 and influenza.[47-49] The pulmonary surfactant phospholipids are thought to prevent viral infections by inhibiting viral binding to epithelial cells. The use of surfactants to achieve the same results in the upper aerodigestive tract is intriguing but has not been studied. One proposed trial aims to investigate the effect of saline irrigations and baby shampoo/saline irrigations on patients with COVID-19.[50] Most surfactants have been reported to have good tolerability, but it is worthy to note that surfactant additive in nasal saline rinses has been associated with nasal congestion and temporary smell loss in healthy volunteers.[51]

UV Radiation

Based on the physiologic effects, UV radiation can be divided as follows: UV-C (100-280 nm), UV-B (280-320 nm), and UV-A (320-400 nm). The majority of evidence of the biological effect of UV light has come from the field of dermatology, where various forms of phototherapy have been applied for decades.[52]

Intranasal phototherapy has been explored for the treatment of other rhinologic conditions, primarily based on its immunomodulating effect on inflammatory processes.

Two RCTs demonstrated that combined low-dose UV-B, low-dose UV-A, and visible light are effective in reducing symptom scores of moderate to severe ragweed-induced allergic rhinitis uncontrolled by antiallergic drugs.[53,54] However, a similar treatment protocol does not appear to have efficacy for treatment effective for chronic rhinosinusitis.[55]

The carcinogenic risk of rhinophototherapy on the nasal mucosa appears to be limited at the exposure levels used in the studies cited. Nasal epithelial cells are capable of repairing UV-induced DNA damage in patients with allergic rhinitis who are receiving intranasal phototherapy.[56] Significant DNA damage was observed immediately after completion of 2 weeks' treatment, which was reduced at the 10-day assessment but equivalent to the control group at 2-month follow-up. Parallel experiments demonstrated similar repair kinetics in human skin in vitro and animal models.[57] Animal studies with UV-A and UV-B irradiation demonstrate no histopathologic changes[58] and no induction of apoptosis at lower doses.[59] Other animal studies have shown similar reduction in histopathologic changes with phototherapy as compared with nasal corticosteroid treatment without increasing apoptosis of mucosal cells.[60]

UV-C is strongly absorbed by the nucleic acids of microorganisms and therefore is the most lethal range of wavelengths for them. UV-C sterilization has been proposed as an effective method for simultaneous disinfection of the water source and saline irrigation bottle[61] and has been used in combination to reduce titers of SARS-CoV-2 to nondetectable levels in human blood transfusion products.[62]

Multiple clinical studies dating back to the 1940s[63] demonstrated that UV exposure of the wound during surgery resulted in markedly decreased surgical site infection rates. However, conventional UV-C light sources, typically emitting at 254 nm, are a human health hazard, causing skin cancer and cataracts.[64,65] In contrast, far-UV-C light in the range of 207 to 222 nm has the same bactericidal potential of 254-nm light but without the damaging effects to mammalian cells and tissues. Due to its short range in biological materials, far-UV-C light does not penetrate the outer layer of the skin or the outer surface of the eyes but can efficiently inactivate the nucleic acids and proliferative capacity of surface microbes.[66,67]

While intranasal UV-A and UV-B light is safe, phototherapy at this wavelength has limited antimicrobial activity. UV-C light is an effective method for sterilization, but the intranasal safety profile for UV-C phototherapy has not been studied.

Oxymetazoline and Xylometazoline

Oxymetazoline and xylometazoline are commonly used over-the-counter nasal decongestants. Adverse effects include local irritation and rhinitis medicamentosa, in which overuse causes paradoxical nasal obstruction. Small studies have shown transient decreased viral load in rhinovirus via topical oxymetazoline nasal spray.[68] These agents have not been studied in other viruses or SARS-CoV-2. Given that they have been shown to reduce rhinovirus viral load, caution may be advisable with their use prior to nasal swab viral testing.

Interferon

Interferons are complex cytokines intricately involved in innate cellular immunity and are named for their ability to interfere with viral replication. Interferons increase expression of major histocompatibility complex (MHC) molecules. Increased MHC I expression upregulates viral presentation to cytotoxic T cells. Stimulation of MHC II expression potentiates helper T-cell response and subsequent release of cytokines that increase activity of other immune cells.[69]

Viral cellular invasion activated type 1 interferons, which secrete fibroblasts and monocytes with interferon-specific receptors. Subsequently, this activates the classical JAK-STAT signaling pathway (Janus kinase–signal transducer and activator of transcription). The downstream result is an expression of proteins that inhibit viral replication.[69] The role of interferon in SARS-CoV-2 is intriguing but duplicitous. The SARS-CoV-2 virus enters the cell following binding of a spike protein domain with the ACE2 receptor, which is upregulated by interferons and has been suggested to help lung cells tolerate damage. However, in the case of SARS-CoV-2, the upregulation of ACE2 may actually exacerbate the disease. It is unclear if SARS-CoV-2 is utilizing the important role of interferon in our innate clinical immunity or if the beneficial effects of interferon outweigh the increased cellular entry that it allows.[70]

Interferons have been investigated for use against SARS-CoV. An in vitro study of cell lines from patients infected with SARS-CoV showed that interferon alpha, beta, and gamma all inhibited SARS-CoV replication; however, interferon beta was 5 to 10 times more effective and showed prophylactic protection as well as antiviral potential after infection.[71] Others suggest that type 3 interferons—specifically, interferon lambda—could be a better therapeutic option in respiratory infections. Sun et al showed that interferon lambda was superior to type 1 interferons due to their specificity in the respiratory tract, thereby decreasing systemic side effects—specifically, an inflammatory response that is sometimes characterized by type 1 interferons.[72]

Aerosolized interferon treatment has been shown to be effective in viral-mediated respiratory disease. Type 1 interferons have been shown to induce undesirable systemic side effects, such as fatigue, headache, pyrexia, myalgia, rigors, and psychiatric symptoms. However, topical formulations of recombinant human interferon alpha-2b have been shown to have no significant systemic side effects.[73] This formulation was used as a topical nasal spray in a placebo-controlled trial in children with hand-foot-and-mouth disease. The children treated with the topical nasal interferon alpha-2b had a shorter duration of fever, fewer oral ulcers, less skin rash, and decreased appetite when compared with the placebo group.[73] A new formulation of type 1 interferon—interferon beta-1a—was used in a double-blind, placebo-controlled trial of patients with asthma in attempts to decrease viral respiratory infections and, thus, asthma exacerbations (NCT 01126177). The proprietary interferon beta-1a formulation is the only aqueous preparation and is pH balanced to the respiratory mucosa, making it an ideal therapeutic for inhalation. Although this study failed to meet its primary end point of better asthma control, it did show good evidence of enhanced innate immunity with increased production of antiviral genes in induced sputum.[74]

Topical interferon is an intriguing target for SARS-CoV-2 therapy. Preliminary results of its use as a prophylactic for health care workers in Hubei, China, show no infections in the 2944 health care workers using the medication as a nasal drop.[75] While well-conducted prospective trials are certainly needed in peer-reviewed literature, this therapy offers immense promise as a well-tolerated, easy-to-deliver topical prophylactic against SARS-CoV-2 infection.

Enhancing Mucosal Absorption Efficiency

The advantages in nasal mucosa as a drug delivery medium include increased absorption rate, possible increased bioavailability through avoidance of hepatic first-pass metabolism, and a less acidic pH environment. However, challenges include poor retention time on membrane, narrow absorption value, degradation via mucolytic enzymes, and continuous mucociliary movement leading to washout.[76]

Chitosan

Chitosan is a cationic polysaccharide widely studied for its mucoadhesive-enhancing properties in medication delivery. Chitosan can contain an array of chemically altered functional groups to enhance mucoadhesive properties and permeation effects via opening of epithelial tight junctions, and several studies have demonstrated superiority in chitosan-bound medications as compared with unbound forms. Currently, chitosan has FDA-approved uses as a wound-healing agent. However, limited study has been conducted on nasal chitosan-based antiviral medications. Given chitosan's flexibility and study as a strong mucoadhesive with generally low toxicity, more research is needed into possible nasal chitosan-based antiviral medications.[77]

Liposomes

Lipophilic/liposomal formulations have aided drug delivery across lipid bilayer cell membranes. Many FDA-approved medications, such as doxorubicin, amphotericin B, and others, have liposomal drug formulations. Several in vitro and in vivo animal studies have found liposomal formulations to improve drug bioavailability across the mucosal membrane barrier. However, despite the significant quantity of research around chitosan and liposomal nasal nanoparticle formulations, there remains no FDA-approved products of chitosan- and liposomal-based nasal drug delivery systems, and further research in humans is needed to support clinical safety and efficacy.[78]

Poloxamers

Poloxamers are a class of hydrogels that are water-soluble and nonionic copolymers with amphiphilic and surface-active properties. Increasing temperature of their aqueous

solutions creates a sol-to-gel transition above a critical gelation temperature. Hydrogels are used to facilitate localized sustained release of a drug, thereby lowering drug dosage, limiting administration frequency, and avoiding adverse effects. Poloxamers are FDA approved as a nontoxic solubilizer, emulsifier, and stabilizer and can be administered through oral, parenteral, and topical routes.[79]

Route and Medium of Drug Delivery

Solution Sprays

Intranasal drug delivery has been used for allergic rhinitis, chronic rhinosinusitis, opioid overdose, and topical anesthesia/decongestion for many years and has been widely studied in the literature.[80] Factors that make this delivery option favorable are the relative ease of use in a home environment and good patient tolerance. The risk of inducing viral shedding is unknown, as these sprays are aerosolized and could elicit sneeze or coughing. Most sprays generate an aerosol that deposits in the anterior nasal cavity, with mucociliary clearance carrying medications deeper into the nasal cavity. Newer exhalation delivery nasal sprays have been shown to distribute farther within the nasal cavity (**Figure 4**).[81] Nasal nebulizers have also been employed in the treatment of chronic rhinosinusitis and nasal polyposis; however, distribution of medication is not significantly different than that of the exhalation delivery systems and has higher associated equipment cost. The mucous layer within the nose renews within 20 minutes and is discarded into the nasopharynx; thus, the speed at which the medication dissolves within the mucous layer and penetrates mucosa is critical for drug efficacy. Computational fluid dynamics could be utilized to determine appropriate particle size, spray velocity, and dosing to help guide effective therapies.

Saline Rinses

Like solution sprays, intranasal saline rinses are widely available, utilized with and without the addition of medications, and generally well tolerated. Further investigation on the risk of viral shedding is needed. Advantages suggested over sprays include the removal of the mucous barrier with the rinse action to provide maximum interface between the drug and the mucosa itself.[82] However, formulations of medications must be water soluble to administer in this method.

Gel

Intranasal nanogels have been utilized for drug delivery in Alzheimer's disease, migraines, depression, and schizophrenia.[83] This medium can be utlizied for hydrophilic and hydrophobic drugs, distinguishing it from the aforementioned intranasal sprays and rinses that typically require a suspension. Additionally, the increased viscosity of the gel formulation may increase the residence time of the drug on the nasal mucosa, therefore increasing drug absorption through the mucosa.[84] Increasing the viscosity may, in turn, interfere with normal ciliary beating and cause untoward negative side effects. Challenges include maintaining stable formulations with consistent dosing while preserving an adequate shelf life and designing an efficient delivery system to administer the gel within the nasal cavity. Wang et al[85] also proposed a hybrid of technologies via an in situ gel-forming system, where a solution instilled intranasally undergoes phase transition to a viscoelastic gel. Advantages of this system include increased retention in the nasal cavity and increased permeability through the mucous membranes.

Foam/Packing

Intranasal foam and dissolvable packing have been utilized for many years by otolaryngologists for treatment of epistaxis, chronic rhinosinusitis, and postsurgical sinus cavities. Applications for drug delivery for psychiatric conditions, such as bipolar disorder and schizophrenia, have also been studied. Examples of intranasal foams include chitosan, carboxymethylcellulose, hyaluronic acid, and synthetic polyurethane foam. Nanoparticles used as reservoirs for hydrophobic drugs can be compounded within these foams to provide increased mucoadhesive properties and enhanced absorption of medications. This method would likely be more challenging for patients to self-administer, as most otolaryngologists employ its use by direct administration by a medical professional rather than by patients themselves. Additionally, these foams are traditionally applied under at least topical anesthesia and may be less tolerated by eliciting more sneezing and irritation than sprays/rinses.

Dry Powders

Most intranasal sprays on the market are liquid suspensions; however, recreational drugs have been used in powder form for many years. More recently, dry mist nasal sprays have been introduced, which dissolves the medication in hydrofluoroalkane propellant. Nonaqueous propellants such as propylene glycol, isopropyl alcohol, and PEG400 are known to cause local irritation with chronic use; thus, careful attention to the choice of propellant and possible adverse reactions must be considered. Other challenges for utilization of powders include being able to distribute within the nasal cavity, controlling the particle size, protecting the powder's viability from humidification during storage, and maximizing absorption by the mucous membranes.[81]

Ointment

Nasal ointments have been in use for control of folliculitis within the nasal vestibule as well as for prevention of epistaxis; however, more recently, interest has increased in drug delivery via nasal ointments, such as that for allergic rhinitis.[86] Via intranasal swabs, these ointments are easily applied by patients to the anterior nasal vestibule, with mucociliary clearance carrying medications farther within the nasal cavity. The higher-viscosity ointments again result in lower tendency to spread and may increase retention time within the nasal cavity. The lipophilic properties of the ointment may also enhance absorption by the nasal mucosa. Disadvantages of ointments, specifically long-chain mineral hydrocarbons, include risk of paraffin granulomas and case reports of lipoid pneumonia from long-term nocturnal intranasal application.[86]

Implications for Practice

Topical intranasal antiviral drug delivery has several potential applications, but further studies are necessary. Efficacy in many settings is currently unknown, and considerations for any potential adverse effects, including loss of taste and smell, epistaxis, and mucosal irritation, are important. For example, while zinc-dependent processes have become a target for SARS-CoV-2 therapies due to its modulating effect on ACE2,[87] a zinc nasal spray was pulled from the market in the past after multiple cases of smell loss became public and a case series described zinc-induced anosmia.[88]

The panel discussed the following settings in which studies of topical intranasal delivery of antiviral medications could be considered (**Figure 5**):

- Perioperative prevention for health care workers and patients
- Prevention of the well person from contracting the virus
- Prevention of the infected person or presymptomatic carriers from spreading the virus
- Systemic drug delivery
- Treatment of intranasal viral disease
- Reduction in progression of viral disease

Perioperative application as an antiseptic is the most mentioned use of intranasal (as well intraoral) antiviral agents. Several articles have described considerations of PI usage during oral and head and neck surgery, as well as in-office application for prevention of viral spread during minor endoscopic procedures, such as diagnostic nasal endoscopy and flexible fiberoptic nasolaryngoscopy.[24,25] While clinical settings are the ideal initial areas for investigation, studies of community populations could be considered for the widespread prevention of spread and as potential therapeutic options for nasal symptomatology.

The nasal cavities and nasopharynx harbor a significant amount of SARS-CoV-2, even in asymptomatic or presymptomatic carriers of the virus. Several possible candidates exist for intranasal delivery of virucidal drugs and agents; however, clinical efficacy would require the agents to have adequate mechanisms of target or viral cellular infiltration with routes of delivery and medium suspension to reach the pathologic areas. Cellular absorption enhancement agents may also be needed to increase effectiveness. As with any therapeutic agent, proper safety profiles for intranasal use are important. This article summarizes the current knowledge from the literature regarding intranasal drug delivery and its potential applications in combating the SARS-CoV-2 pandemic and other future viral epidemics.

Author Contributions

Thomas S. Higgins, concept, design, interpretation, drafting, revising, final approval, agreement to be accountable; **Arthur W. Wu**, concept, design, interpretation, drafting, revising,

final approval, agreement to be accountable; **Elisa A. Illing**, concept, design, interpretation, drafting, revising, final approval, agreement to be accountable; **Kevin J. Sokoloski**, concept, design, interpretation, drafting, revising, final approval, agreement to be accountable; **Bree A. Weaver**, concept, design, interpretation, drafting, revising, final approval, agreement to be accountable; **Benjamin P. Anthony**, concept, design, interpretation, drafting, revising, final approval, agreement to be accountable; **Nathan Hughes**, concept, design, interpretation, drafting, revising, final approval, agreement to be accountable; **Jonathan Y. Ting**, concept, design, interpretation, drafting, revising, final approval, agreement to be accountable.

Disclosures

Competing interests: Thomas S. Higgins, Sanofi/Regeneron (advisory board, speaker), Genentech (advisory board), Optinose (speaker, investigator), Gossamer (investigator), IntersectENT (speaker), Acclarent (speaker); Arthur W. Wu, Sanofi/Regeneron (advisory board, speaker), Optinose (speaker, investigator), Gossamer (investigator); Bree A. Weaver, Gilead (advisory board), Pfizer (stock), Johnson & Johnson (stock).

Sponsorships: None.

Funding source: None.

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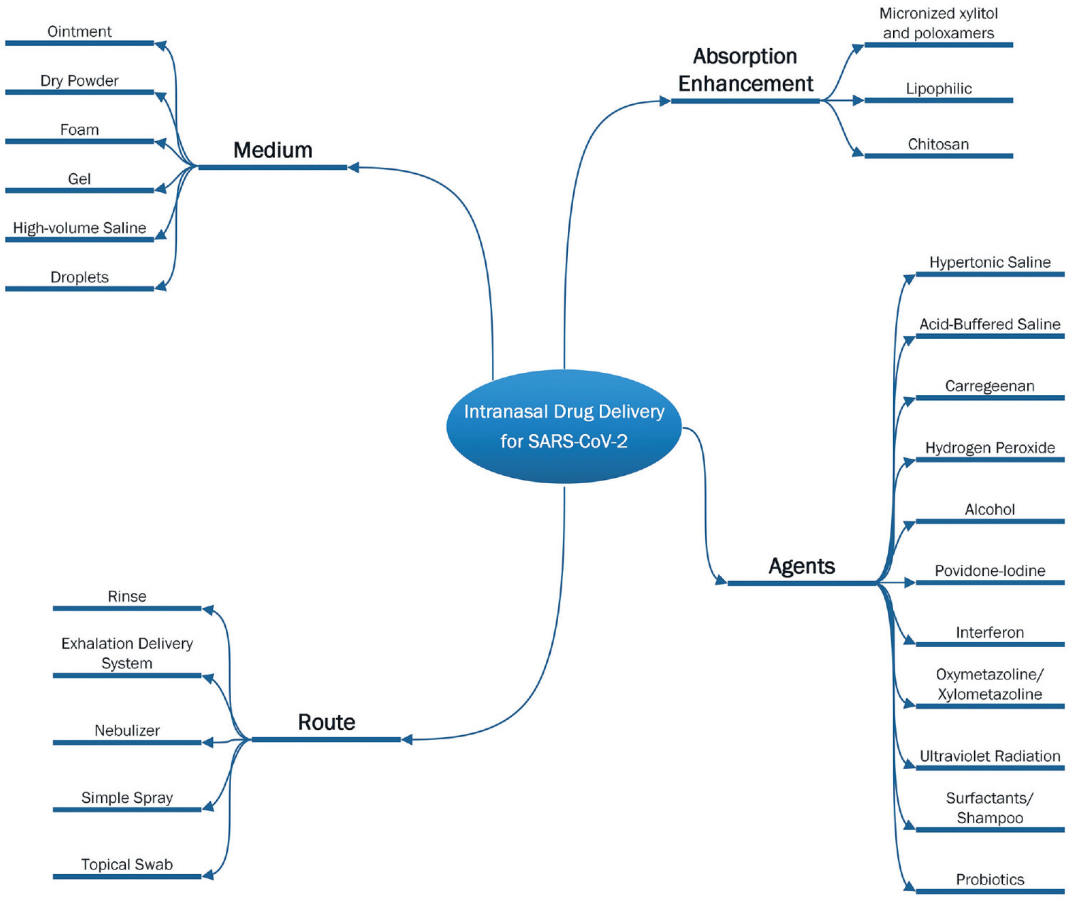

Figure 1. Mind map displaying the ideas and concepts of intranasal drug delivery in the setting of antiviral disease, including SARS-CoV-2. The central topic has branches extending radially to connect subtopics. Each subtopic is connected to key concepts.

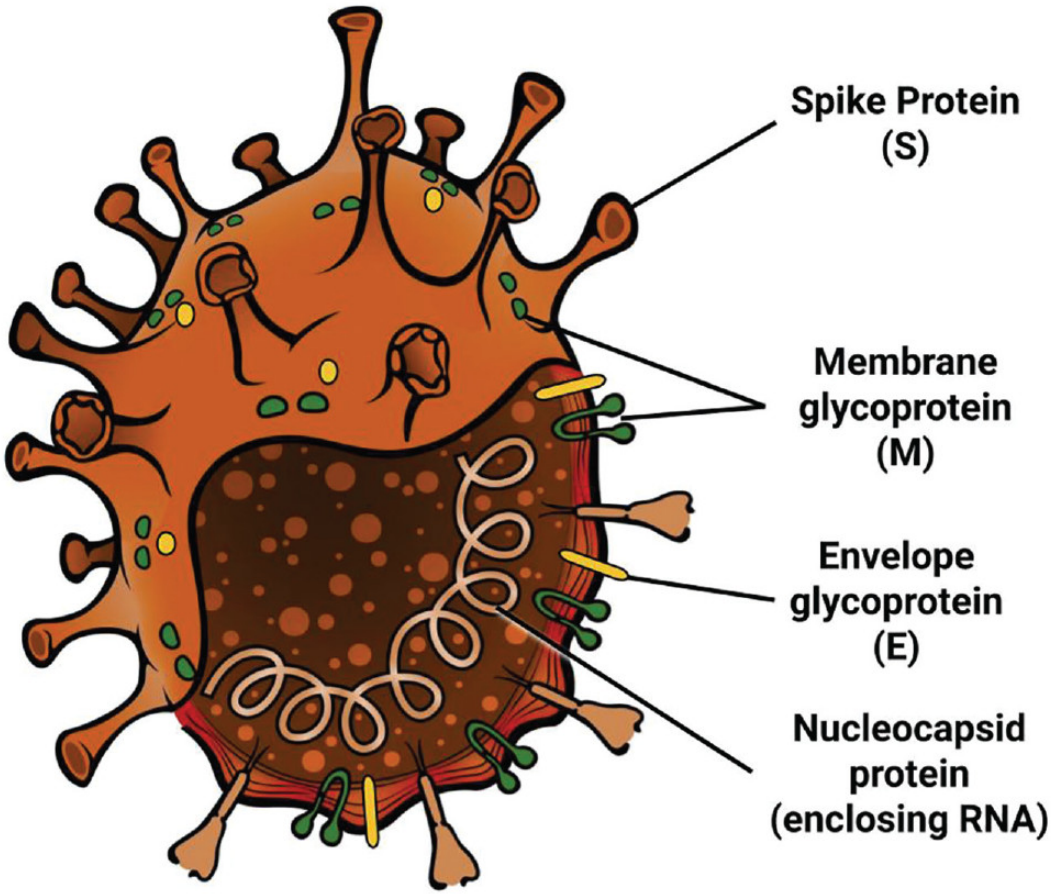

Figure 2. Structure of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

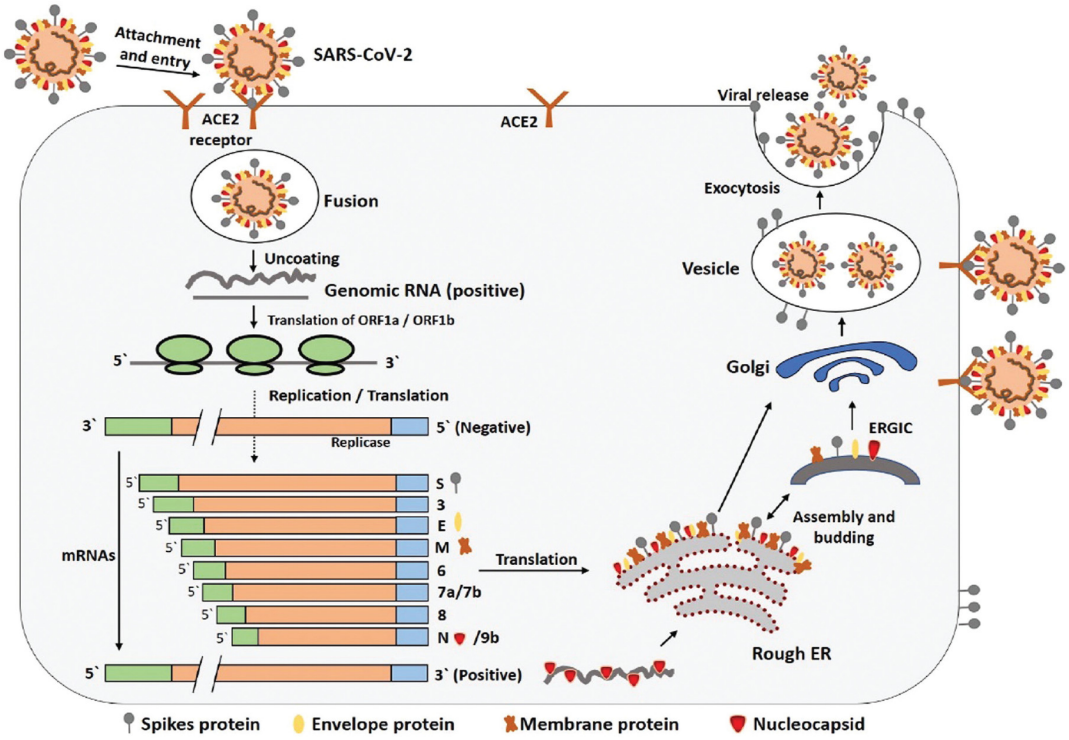

Figure 3. The life cycle of SARS-CoV-2 in host cells. ACE2, angiotensin-converting enzyme 2; ER, endoplasmic reticulum; ERGIC, ER–Golgi intermediate compartment. Reprinted from Shereen et al (2020).8

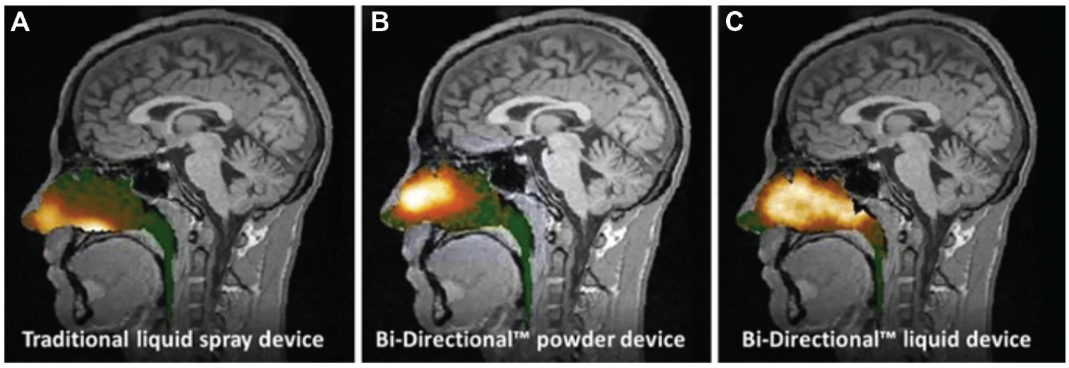

Figure 4. Gamma camera image information from the nasal cavity superimposed on the corresponding sagittal MRI section presenting deposition two minutes after delivery using: (A) a traditional liquid spray, (B) the breath-powered powder device, and (C) the breath-powered liquid spray device incorporating the same spray pump. Reprinted from Djupesland et al (2012).81

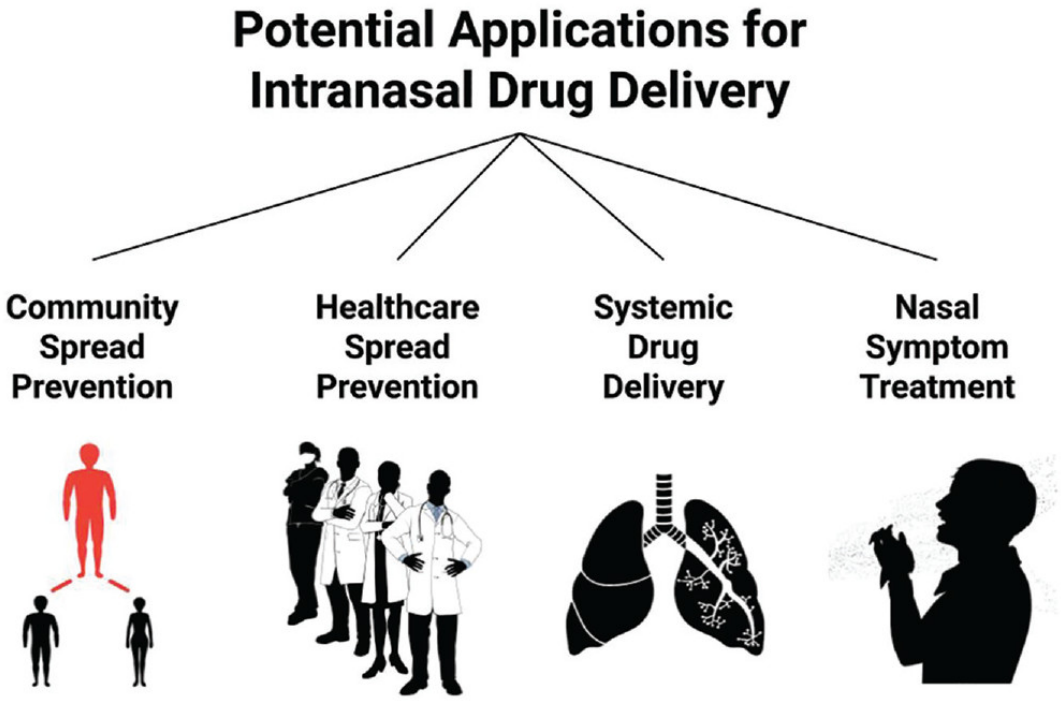

Figure 5. Potential applications of intranasal drug delivery.

Table 1. Evidence for Topical Intranasal Antiviral Therapies.

Agents (antiviral mechanism)							
SARS-CoV-2			Other viruses				
In vitro activity	In vivo activity	Clinical efficacy	In vitro activity	In vivo activity	Clinical efficacy	Adverse reactions [a]	Conclusion
Alcohol and isopropanol (virucidal)							
+	NS	NS	+, SARS-CoV-1, MERS-CoV	NS	NS	+: I; NS: ST, H, A, B, F, RS	Alcohol and isopropanol surface preparations have rapid virucidal effects on SARS-CoV-2 and other viruses, but they can cause nasal irritation. An intranasal swab application has shown antibacterial properties without nasal irritation.
Hydrogen peroxide (virucidal)							
+	NS	NS	+	NS	NS	NS: I, ST, H, A, B, F, RS	H_2O_2 has long been used as a disinfecting agent and has efficacy against SARS-CoV-2 and other viruses in vitro. Intranasal safety profile is unknown.
Povidone-iodine (virucidal)							
+	NS	NS	+, MERS-CoV, SARS-CoV-1, H1N1	NS	NS	+: I (5%), A; –: I (S0.5%); NS: ST, H, A, B, F, RS	Anterior nasal formulations are tolerated well. In vitro preparations have shown rapid virucidal effects to SARS-CoV-2 and other viruses. Human adverse effect profile is incomplete. Povidone-iodine may have ciliotoxic effects and smell/taste loss has not been evaluated.
Carrageenan (prevents viral attachment)							
NS	NS	NS	+, rhinovirus, enterovirus, influenza	+, rhinovirus	+, rhinovirus	NS: ST, H, A, B, F, RS	Carrageenan nasal sprays have shown efficacy in reducing viral loads and symptoms versus placebo in several randomized controlled trials. No nasal irritation were noted, but other adverse effects were not evaluated.
Acid-buffered saline (virucidal)							
NS	NS	NS	+	+, rhinovirus, influenza	+, rhinovirus	NS: ST, H, A, B, F, RS	Acid-buffered saline nasal gels have been used in several studies demonstrating ability to reduce viral load and symptoms.
Hypertonic saline (promotes innate antiviral immune response)							
NS	NS	NS	+	+, common cold	+, common cold	+: I, H, B; NS: ST, A, F, RS	Hypertonic saline irrigation is well tolerated with minor discomfort in many other diseases and has been shown to reduce symptoms, viral shedding, and transmission of the common cold.

Table 1. (continued)

Agents (antiviral mechanism)							
SARS-CoV-2			Other viruses				
In vitro activity	In vivo activity	Clinical efficacy	In vitro activity	In vivo activity	Clinical efficacy	Adverse reactions [a]	Conclusion
Probiotics (may promote innate immunity and antibody production)							
NS	NS	NS	+	+	+, rhinovirus, influenza	+: I; NS: ST, H, A, B, F, RS	Nasal probiotics have been shown to be well tolerated in chronic rhinosinusitis but have not been studied for antiviral purposes. Oral probiotics have shown efficacy in animal and human studies with common upper respiratory viruses
Surfactants/shampoo (prevents viral plasma membrane fusion)							
NS	NS	NS	+	+, H1N1, influenza	NS	+: I, ST; NS: H, A, B, F, RS;	Surfactant has been shown in vitro and in vivo (lungs) to have antiviral properties. Nasal surfactant or shampoo rinses are usually well tolerated but have had reports of nasal irritation and reversible smell loss. Intranasal surfactant efficacy against viruses has not been studied.
UV (virucidal)							
+	NS	NS	+	NS	NS	NS: I, ST, H, A, B, F, RS	UV-C radiation is virucidal to SARS-CoV-2, but its use intranasally and its safety profile have not been studied. Far UV-C light may be less harmful but retain its antimicrobial properties.
Oxymetazoline and xylometazoline (unknown)							
NS	NS	NS	NS	+	+	+: I; NS: ST, H, A, B, F, RS	Small study shows that nasal decongestant may reduce viral shedding temporarily in rhinovirus. Extended use is known to cause mucosal irritation and rebound nasal congestion.
Interferon (multiple pathways)							
NS	+	+	+, SARS-CoV-1	+, HFMD, influenza	+, HFMD	NS: ST, H, A, B, F, RS	Systemic interferon induces multiple side effects, but intranasal preparations have been shown to have antiviral properties and be well tolerated. Topical nasal drops were used as prophylaxis in health care workers in Hubei, China, during the beginning of the epidemic with no infections recorded in this population.

Abbreviations: +, yes, there is evidence; –, no, there is evidence against statement; HFMD, hand-foot-mouth disease; MERS-CoV, Middle East respiratory syndrome coronavirus; NS, not studied; SARS-CoV, severe acute respiratory syndrome coronavirus; UV, ultraviolet.

[a]Mucosal or skin irritation (I), smell and taste disturbance (ST), headaches (H), allergic reactions (A), nasal bleeding (B), fungal infection or colonization (F), and rhinosinusitis (RS).